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Sale-based estimation of pharmaceutical concentrations and associated environmental risk in the Japanese wastewater system

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ABSTRACT

Information on sales and emission of selected pharmaceuticals were used to predict their concentrations in Japanese wastewater influent through a > 300 of pharmaceuticals data sink. A combined wastewater-based epidemiology and environmental risk analysis follow was established. By comparing predicted environmental concentrations (PECs) of pharmaceuticals in wastewater influent against measured environmental concentrations (MECs) reported in previous studies, it was found that the model gave accurate results for 17 pharmaceuticals (0.5 < PEC/MEC < 2), and acceptable results for 32 out of 40 pharmaceuticals (0.1 < PEC/MEC < 10). Although the majority of pharmaceuticals considered in the model were antibiotics and analgesics, pranlukast, a receptor antagonist, was predicted to have the highest concentration in wastewater influent. With regard to the composition of wastewater effluent, the Estimation Program Interface (EPI) suite was used to predict pharmaceutical removal through activated sludge treatment. Although the performance of the EPI suite was variable in terms of accurate prediction of the removal of different pharmaceuticals, it could be an efficient tool in practice for predicting removal under extreme scenarios. By using the EPI suite with input data on PEC in the wastewater influent, the PEC values of pharmaceuticals in wastewater effluent were predicted. The concentrations of 26 pharmaceuticals were relatively high (> 1 μg/L), and the PECs of 6 pharmaceuticals were extremely high (> 10 μg/L) in wastewater effluent, which could be attributed to their high usage rates by consumers and poor removal rates in wastewater treatment plants (WWTPs). Furthermore, environmental risk assessment (ERA) was carried out by calculating the ratio of predicted no effect concentration (PNEC) to PEC of different pharmaceuticals, and it was found that 9 pharmaceuticals were likely to have high toxicity, and 54 pharmaceuticals were likely to have potential toxicity. It is recommended that this is further investigated in detail. The priority screening and environmental risk assessment results on pharmaceuticals can provide reliable basis for policy-making and environmental management.

1. Introduction

Pharmaceuticals are contaminants of emerging concern due to their potential threat to the aquatic ecosystem and human health (Boxall et al., 2012; Ebele et al., 2017; Schwarzenbach et al., 2006). Pharmaceuticals comprise a large, diverse group of compounds, including antibiotics, hormones, anti-inflammatory drugs, antiepileptic drugs, blood lipid regulators, β-blockers, contrast media, and cytostatic drugs (Mehrabad et al., 2016). Effluent from wastewater treatment plants (WWTPs) is the main source of pharmaceuticals released into the environment (Daughton and Ternes 1999), and reported pharmaceutical concentrations in wastewater treatment systems range from ng/L to μg/L (Verlicchi et al., 2012). Due to their limited removal efficiency by conventional wastewater treatment processes, a large number of residual pharmaceuticals are discharged from WWTPs, and contaminate receiving water bodies. According to previous studies, diclofenac was

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widely detected in aquatic environments around the world, and it was indicated to have high environmental risk in aquatic environments as well as ethinylestradiol and atorvastatin (Singh et al., 2019; Zhou et al., 2019). Besides, given that many drinking water treatment plants (DWTPs) use source water impacted by wastewater, a possible health risk may exist in drinking water contaminated with pharmaceuticals and personal care products (PPCPs) (Benotti et al., 2008). Traces of pharmaceutical pollution have been found in Canada, Germany, Italy, UK, and the USA (Jones et al., 2005; Zwiener, 2007). Therefore, monitoring pharmaceuticals in wastewater is of vital importance in identifying (and hence addressing) both environmental risk and human risk.

Highly sensitive analytical techniques, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), are used to monitor pharmaceutical concentrations in wastewater. Determination of all pharmaceuticals in a wastewater sample is necessary to estimate accurately the overall risk due to their presence. However, this involves complex pretreatment, expensive operating costs, and lengthy analysis (Petrović et al., 2005), which suggests that a method based on selected, priority pharmaceuticals in wastewater would be beneficial to screen the priority of pharmaceuticals considering the environmental risk. Moreover, Ottmar et al. found that cited scientific research had not considered prescription frequency or daily load, indicating a gap in understanding of the actual situation of pharmaceutical pollution (Ottmar et al., 2010). Thus, a comprehensive strategy for evaluation of priority pharmaceuticals in wastewater is necessary to restrict monitoring to a limited number of the most hazardous drugs. Several studies have estimated the predicted environmental concentration (PEC) of pharmaceuticals in receiving water in order to determine their priority order. For example, the average consumption of paracetamol and metformin, the most commonly prescribed pharmaceuticals in the UK, was used to predict their environmental concentrations of 11.96 and 6.30 μg/L, respectively (Jones et al., 2002). In China, 13 pharmaceuticals were classified as priority pharmaceuticals based on available consumption data (Li et al., 2019). Gómez-Canela et al. prioritized the occurrence of pharmaceuticals in rivers in Catalonia according to pharmaceutical consumption data (Gómez-Canela et al., 2019).

In calculating the PEC of pharmaceuticals in receiving water, three relevant factors should be considered: pharmaceutical consumption, excretion rate, and the removal efficiency of WWTPs. Pharmaceutical consumption is calculated from data on the sales of pharmaceuticals, obtained from medical authorities. In practice, when pharmaceuticals are excreted after metabolism, a variety of metabolites enter the wastewater sewage system together with their parent compounds in urine and feces. Hence, it is necessary to consider the excretion efficiencies by which PECs become refined, i.e., the percentage of the drug excreted with respect to its parent compound. To date, the PEC of pharmaceuticals in effluent has been investigated using factors related to consumption and measured removal efficiencies in target WWTPs (Alder et al., 2010). The occurrence of pharmaceuticals in surface waters has also been evaluated, with the results showing that concentrations of pharmaceuticals correlated well with consumption data (Scheurer et al., 2009; ter Laak et al., 2010). The findings indicate that, among other criteria, international or national sales data can be a valuable resource from which to select relevant pharmaceuticals for monitoring and hence to estimate loads and average environmental concentrations in wastewater. In Japan, the occurrence of pharmaceuticals in the wastewater system has been evaluated in previous studies, in particular during the period from 2007 to 2009, when analgesics (i.e., acetaminophen) and antibiotics (i.e., ampicillin) were detected at high concentrations (Kim et al., 2009; Kobayashi et al., 2006; Nakada et al., 2007; Narumiya et al., 2009). Two prediction studies of pharmaceuticals in wastewater have been performed in Japan (Azuma et al., 2015; Suzuki, 2012), with estimated concentrations of 15 and 7 pharmaceuticals respectively; in both cases, the number of target pharmaceuticals was limited. Obviously, more pharmaceuticals should be selected to enhance accurate prediction in Japan.

Previous studies mainly focused on the well-investigated pharmaceuticals, while the priority of some important but high environmental risk pharmaceuticals could be ignored, and these compounds were carefully investigated in this study. Moreover, a huge data source including > 300 pharmaceuticals with different varieties in pharmacologic classification were applied, and a great many information of these pharmaceuticals were provided for calculation. Furthermore, a novel analysis work flow integrating wastewater-based epidemiology and environmental risk was established, which was from sale data of pharmaceuticals, to their environmental risks, and then to screening the priority of pharmaceuticals. The overall aim of this study is to develop a predictive approach to estimate pharmaceutical concentrations in the Japanese wastewater system by using pharmaceutical industrial sales data and to apply this approach to assess the environmental risk of pharmaceutical contamination. First, an updated list of priority pharmaceuticals was obtained in terms of sales volume, and their PECs in wastewater influent were estimated with respect to excretion rate from the human body and compared against measured environmental concentrations (MECs). Second, after evaluating the feasibility of removal by comparing reported and predicted removal efficiencies of pharmaceuticals in WWTPs, the predicted concentrations of PPCPs in wastewater effluent were estimated. Finally, the environmental risks posed by different pharmaceuticals were evaluated from their PECs in wastewater systems, and priority pharmaceuticals proposed in terms of environmental risk.

2. Methods

2.1. Pharmaceutical discharge loads

Discharge loads of pharmaceuticals in wastewater were calculated from sales data on pharmaceuticals in Japan, based on the sale yield of pharmaceuticals rather than usage by patients. Sales volumes of over-the-counter drug (OTC) pharmaceuticals in terms of numbers of packs sold per year were obtained from statistics compiled by Japanese Ministry of Health, Labour and Welfare in 2014, which was public from 2017 (Ministry of Health, Labour and Welfare, 2018). Although the local sale data could improve the prediction performance locally, the national sale data can provide the priority pharmaceuticals from the perspective of national policymaking. In addition, the yearly change of pharmaceutical consumption and the consumption behavior of pharmaceuticals in Japanese local area were shown in Figs. S1 and S2, indicating that Japan has relatively stable pharmaceutical consumption in time and space. Furthermore, the concentration of pharmaceutical in wastewater influent was strongly related to the water consumption. The average water consumption in Japan was approximately 300 L per capita, per day with the range of 267 (lowest)–338 (highest) L per capita, per day, which indicated the water consumption fluctuated around 10%. Thus, the national sale data were applied in this study.

2.2. PECs of pharmaceuticals in wastewater influent

Following European Medicines Agency (EMA) guidelines (Huschek et al., 2004), PECs in wastewater influent ($PEC_{\text{inf, EMA}}$) were estimated from per capita annual consumption in Japan using the following formula:

$$PEC_{\text{inf, EMA}} = \frac{A}{365 \times P \times V} \quad (1)$$

where A is the annual sale amount of pharmaceuticals in Japan (kg per year), P is the population in the area, and V is the volume of wastewater per capita, per day (0.3 m^3) (Ministry of Economy Trade and Industry, Japan, 2010; Ogawa 2006). The population (P) in Japan was set as 125,583,658, according to the Japanese government report (Statistics Bureau of Japan, 2017). However, this formula does not consider the influence of the excretion rate. To improve the predictions, the effect of

excretion efficiencies (f) of pharmaceuticals from humans was incorporated in the calculation of PEC in the influent (PEC_{inf}), indicating the actual amount of active substances entering the sewage system:

$$PEC_{inf} = \frac{A}{365 \times P \times V} \times f \quad (2)$$

Data on renal excretion efficiencies of humans were obtained from the Pharmaceuticals and Medical Devices Agency, Japan (Pharmaceuticals and Medical Devices Agency, 2019), the Japan Pharmaceutical Information Center (Japan Pharmaceutical Information Center, 2004), the KEGG (Kyoto Encyclopedia of Genes and Genomes) database (Kanehisa et al., 2016), Drugbank (Wishart et al., 2017), and previous studies (National Information Program on Antibiotics, 2016; Down et al., 1974; Furuta et al., 2002; Green et al., 2015; Gregory et al., 1993; Naito and Yoshikawa 2010; Rhee et al., 2013; Sakashita et al., 1993; Spratto and Woods 2010; Teramoto et al., 2013; Wang et al., 2012). The details of excretion efficiencies were presented in Supplementary material. Given the variation in the reported values of excretion efficiency, we selected the highest value to account for the most extreme case. For those pharmaceuticals where excretion efficiencies could not be found in databases or the open literature, we set the excretion efficiency to 100% for the most extreme case. In Japan, the average retention time of wastewater in sewage system is generally less than 6 h (Kanagawa Sewerage Work Foundation, 2019), indicating that the pharmaceuticals and their metabolites can be degraded in the WWTPs with relatively short time, so the transformation of pharmaceuticals can be expected in WWTPs.

To clearly illustrate the calculation of PEC_{inf}, the example of sulpiride was provided as follows: Firstly, the sale of sulpiride was calculated by the sale data of commercially available tablets and capsules including 26,795,000 tablets of 100 mg, 373,075,000 tablets of 50 mg and 28,795,000 capsules of 50 mg (Ministry of Health, Labour and Welfare, 2018), indicating that the total yearly amount of sulpiride in Japan was 22,773 kg; Secondly, the excretion efficiencies of sulpiride was 70%, indicating the excreted amount of sulpiride was 15,941 kg; Thirdly, the concentration was calculated by excreted amount, water consumption, and population as shown in Equation (2), so the PEC_{inf} of sulpiride was calculated to be 1159.23 ng/L.

In evaluating model performance, the ratio of PEC to MEC was used to establish whether the prediction underestimated or overestimated the concentration of each pharmaceutical (Verlicchi et al., 2014). The values of MECs in wastewater influent were obtained from previous studies (Azuma et al., 2015, 2016; Kobayashi et al., 2006; Nakada et al., 2007; Narumiya et al., 2009; Suzuki, 2012), and the average concentration of the individual pharmaceutical in several previous studies was used as MEC value in this study. An important influence factor is the difference between reported and actual consumption (Oosterhuis et al., 2013), which could be enhanced by the incomplete use of sold pharmaceuticals and pharmaceuticals obtained from other sources (Ruhoy and Daughton, 2008). In addition, the temporal consumption behavior of pharmaceuticals also influences model predictions (You et al., 2015). Researchers have therefore employed certain criteria related to PEC/MEC to evaluate the prediction results. For example, Morasch et al. and Tauxe-Wuersch et al. adopted the following criteria to classify PEC: 0.1 < PEC/MEC < 10, acceptable (Morasch et al., 2010; Tauxe-Wuersch et al., 2005); PEC/MEC < 0.1, unacceptably low; PEC/MEC > 10, unacceptably high. Stricter criteria were proposed by Ort et al.: 0.5 < PEC/MEC < 2, acceptable, PEC/MEC < 0.5, unacceptably low; and PEC/MEC > 2, unacceptably high (Ort et al., 2009). Table 1 lists the criteria used in the present study in order to classify PEC.

2.3. PECs of pharmaceuticals in wastewater effluent

Pharmaceutical concentrations in wastewater influent indicate consumption habits in the study area, and the environmental risk posed by pharmaceuticals in receiving water relates to their concentrations in wastewater effluent, which are in turn strongly correlated to the removal performance of WWTPs. In practice, activated sludge is the most prevalent treatment technology in WWTPs in Japan (Japan Sewage Works Association, 2016), and so was taken to be the target process in the present study. First, concentrations of pharmaceuticals in the influent and the effluent of Japanese WWTPs that use the activated sludge process based on previous studies were collated (Azuma et al., 2015; Kobayashi et al., 2006; Nakada et al., 2007; Narumiya et al., 2009; Suzuki, 2012), and the measured removal efficiencies were then calculated. Predicted removal efficiencies of pharmaceuticals in activated sludge were computed using the STP script program in the US EPA's Estimation Program Interface (EPI) Suite that is widely used to predict physicochemical properties and removal efficiencies of target contaminants in WWTPs (Lu et al., 2019; Lu et al., 2017). This STP script program provided the removal prediction in WWTPs based on the typical activated sludge conditions. Although parameters in this script program can be set for prediction, such as half-lives in the primary clarifier, aeration vessel and setting tank, the output of BIOWIN script in EPI suite and EPA draft method was used in this study. Model performance was evaluated by comparing predicted and reported removal efficiencies. In the STP script, the BIOWIN output and the EPA draft method for assigning half-lives were used to predict biodegradation and sorption in activated sludge. In order to evaluate the performance of predicted removal efficiencies by EPI Suite, the criteria of removal efficiencies was referred to Table 1.

Table 1
Criteria used to classify PEC.

PEC evaluation	PEC/MEC ratio
Unacceptably high	PEC/MEC > 10
Acceptably high	2 < PEC/MEC < 10
Accurate	0.5 < PEC/MEC < 2
Acceptably low	0.1 < PEC/MEC < 0.5
Unacceptably low	PEC/MEC < 0.1

The PEC of each pharmaceutical in the wastewater effluent was calculated from:

$$PEC_{eff} = PEC_{inf} \times R \quad (3)$$

where R is the removal efficiency predicted by the EPI suite.

2.4. Environmental risk assessment

Pharmaceutical toxicity data were collected from simulated values obtained using ECOSAR developed by US EPA (Sanderson and Thomsen, 2007), and the KAshinhou Tool for Ecotoxicity (KATE), an ecotoxicity prediction system based on quantitative structure-activity relationship (QSAR) models with log P (Furuhama et al., 2011; Melnikov et al., 2016), developed by the Center for Health and Environmental Risk Research (CHERR) of the National Institute for Environmental Studies (NIES), Japan. No-observed effect concentration (NOEC) and effective concentration (EC) (possessing a given percentage effect, generally 50% effect or EC50) values were compared and the lowest value divided by an appropriate assessment factor (10) to give the predicted no-effect concentration (PNEC) (Caldwell et al., 2019). Referring to previous studies (Ma et al., 2016; Zeng et al., 2018), the toxicity was divided into 4 levels with respect to the ratio R_t = MEC/PNEC as follows: high risk ($R_t > 1$), medium risk ($0.1 < R_t < 1$), low risk ($0.01 < R_t < 0.1$), and no risk ($R_t < 0.01$).

3. Results and discussion

3.1. Evaluation of PECs with MECs in wastewater influent

Table S1 in Supplementary material lists the measured and

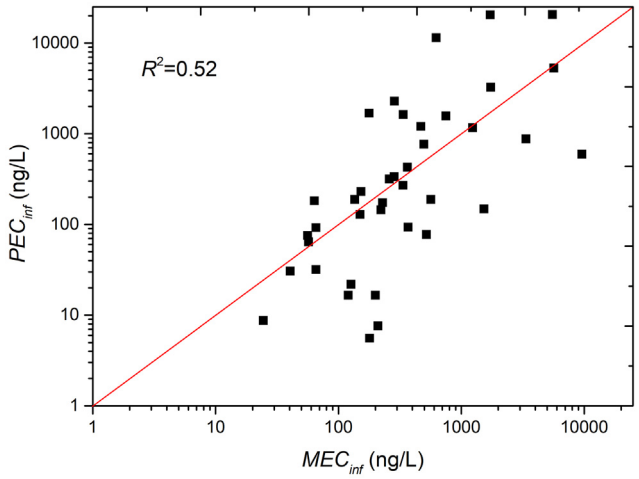

Fig. 1. Comparison between predicted PEC_{inf} and measured MEC_{inf} in wastewater influent.

predicted environmental concentrations of pharmaceuticals in wastewater influent. Fig. 1 is a scatter plot comparing the predicted and measured environmental concentrations of the selected compounds from which it can be readily seen that the predictions of most of the pharmaceutical PECs are acceptable. The correlation coefficient of the logarithmic relationship between the PEC and MEC values is 0.52, indicating the feasibility of the concentration prediction method based on pharmaceutical consumption. Based on the evaluation criteria listed in Table 1, we found that 32 out of 40 (80.0%) reported pharmaceutical PECs were acceptable, and 17 out of 40 (42.5%) pharmaceuticals had accurate PECs, including aspirin (0.86) and disopyramide (1.18). Similar trends were observed in the work by Coetsier et al. who reported that predicted data were acceptable in 36% of cases considered (11 pharmaceuticals) (Coetsier et al., 2009). Metcalfe et al. compared the PEC and MEC of four β-blockers, and found that they had obtained acceptable data at 44% of their sampling points (Metcalfe et al., 2008). The high level of acceptable predictions made by the present study may be attributed to high sewage coverage (78.8%, the ratio of population served by the sewage system to the total population, expressed as a percentage) (Japan Sewage Works Association, 2019) and the high usage of separate sewage systems in Japan. Differences between PECs and MECs could be attributed to the discharge of pharmaceuticals in the wastewater system and consumption from illegal sources (i.e. clandestine manufacturing of pharmaceuticals). Thus, by basing the prediction method on pharmaceutical sales rather than consumption, factors such as unexpected data (i.e. pharmaceuticals distributed without prescription or via hospitals) were avoided (Winker et al., 2008). It should be noted however that Ort et al. observed that national consumption figures do not take into account drugs dispensed to public hospital inpatients departments (Ort et al., 2010); this source of inaccuracy could affect the present study. In addition, transformation of pharmaceuticals by the retention in sewage and temporal variations in pharmaceutical consumption would contribute to the discrepancies between sales and influent concentrations (ter Laak et al., 2010; Oosterhuis et al., 2013). Moreover, national sales data could be inaccurate if local consumption patterns differ from those reported in the national sales data. Hence, we recommend the use of regional consumption data instead of national data if different consumption patterns are expected. Even though the collection and analysis of regional data are potentially difficult tasks, big data technology could facilitate the future direction of such pharmaceutical retrospective approaches. Overall, based on the results in Table S1 and Fig. 1, the foregoing work has resulted in an acceptable tool for the prediction of pharmaceutical concentrations based on sale information, which will be used for the PEC calculation in the following section.

3.1.1. Analgesics/anti-inflammatories

Of the reported pharmaceuticals in Japan, analgesics/anti-inflammatories (i.e., acetaminophen, salicylic acid, and salicylamide) are abundant in wastewater influent (> 100 ng/L) (Azuma et al., 2019a,b; Hanamoto et al., 2018; Narumiya et al., 2009). Other studies on the occurrence of pharmaceuticals in wastewater influent (i.e., United States and China) have reported similar findings (Kostich et al., 2014; Liu and Wong, 2013). Azuma et al. detected loxoprofen, a nonsteroidal anti-inflammatory drug (NSAID), at high concentration of 5.663 μg/L in wastewater influent (Azuma et al., 2016); this value was similar to the PEC of 5.313 μg/L, with PEC/MEC of 0.94. Among analgesics, besides loxoprofen, the PECs of aspirin and disopyramide were also found to be accurately predicted with PEC/MEC of 0.86 and 1.18, respectively. The PEC values for ibuprofen, naproxen, and ketoprofen were acceptably low (0.1 < PEC/MEC < 0.5). Acetaminophen is a traditional analgesic/anti-inflammatory commonly used worldwide, and widely detected at relatively high concentrations in wastewater influent (Burns et al., 2018; Du et al., 2014). However, acetaminophen exhibited a significant difference between its PEC (593 ng/L) and its MEC (9594 ng/L). Similarly, mefenamic acid showed considerable difference in its PEC and MEC values, with PEC/MEC = 0.03. The PECs of acetaminophen and mefenamic acid were unacceptably low. Overall, although the PECs of most analgesics/anti-inflammatories were acceptable, their PEC values were lower than their MEC values in the wastewater influent. For analgesics/anti-inflammatories, which are traditional household pharmaceuticals, their improper disposal (i.e., by flushing them down into the sewage system or discarding them with household waste) increased MEC in wastewater influent and disrupted the model prediction accuracy (Mankes and Silver, 2013). In this case, the analgesics/anti-inflammatories bypassed human metabolism, contributing to the high MEC of analgesics/inflammatories in wastewater influent.

3.1.2. Antibiotics

Antibiotics are another abundant group of pharmaceuticals found in wastewater influent (Guerra et al., 2014). For example, clarithromycin and levofloxacin have been detected at high concentrations (> 400 ng/L) (Hanamoto et al., 2018; Narumiya et al., 2009). For macrolide antibiotics, such as clarithromycin, roxithromycin, and azithromycin, their predicted influent concentrations are close to the measured values (with PEC/MEC ranging from 0.66 to 2.09), confirming that both the consumption pattern and excretion factor are properly modeled. In addition to macrolide antibiotics, PECs of sulfamethoxazole, thiamphenicol, and trimethoprim were found to be accurate, with PEC/MEC ratios of 1.51, 1.54, and 1.40, respectively. Furthermore, the PEC/MEC ratio of ampicillin was 9.47, indicating an acceptably high PEC in wastewater influent. Ampicillin is a common β-lactam antibiotic used to prevent and treat bacterial infections; the hydrolysis of β-lactam antibiotics has been reported in wastewater (Mitchell et al., 2014). Once ampicillin is excreted into the sewage system, its effective hydrolysis could contribute to its elimination, thus affecting the accuracy of the PEC. For ofloxacin (excretion rate of 64%) (Dave and Morris, 2016), the PEC value in wastewater influent was far lower than the measured concentration (PEC/MEC < 0.1), indicating that some other sources of contamination had not been considered in the prediction method. For example, improper disposal or unregistered sources (veterinary medicine), as mentioned previously, could contribute to an increased MEC in wastewater influent.

3.1.3. Receptor antagonists/blockers

In addition to analgesics/anti-inflammatories and antibiotics, antagonists are another important group of pharmaceuticals. In the present study, diphenhydramine, sulpiride, atenolol, and pirenzepine were detected at concentrations of 1530.0, 1234.3, 364.3, and 40.5 ng/L, with corresponding PEC/MEC ratios of 0.10, 0.94, 1.17, and 0.75, indicating their PECs in wastewater were acceptable. The results are

consistent with those reported by Metcalfe et al. (Metcalfe et al., 2008). The stability of these pharmaceuticals in sewer systems is likely to have contributed to their acceptable prediction (Phung et al., 2017).

3.1.4. Others

For other reported pharmaceuticals, the PEC values of amantadine (anti-Parkinson), carbamazepine (anticonvulsant), dipyridamole (antithrombotic), and bezafibrate (antilipemic) in wastewater influent are close to the measured ones, and the ratios of PEC/MEC were 1.22, 1.35, 0.80, and 1.87, respectively. These pharmaceuticals are drugs for treating specific diseases, and they are strictly controlled by government agencies, implying that their consumption is strongly related to their reported sales. In addition, their stability in sewage (i.e., poor biodegradability of carbamazepine and its metabolites) can reduce the influence of sewers on concentration prediction. Thus, the consumption pattern and excretion efficiencies adopted in the calculation could be considered acceptable for their prediction in wastewater influent.

3.2. Prioritization of pharmaceuticals in wastewater influent

Chemical analysis of exogenous biomarkers of drug consumption in wastewater has been shown to have promise for studying drug use within a defined population (Thomas and Reid, 2011). For example, Ong et al. demonstrated through the use of target pharmaceuticals in wastewater plants that the major groups in Australia are heart medications and statins (lipid-lowering agents) (Ong et al., 2018). Considering the environmental risk of priority pharmaceuticals, an approximation using a calculation method would be very helpful. Hence, the PECs were estimated of pharmaceuticals listed in the Japanese Annual Report on Pharmaceutical Industries (Ministry of Health, Labour and Welfare, Japan, 2018), and a reverse analysis developed of wastewater based on epidemiology (using the prediction model described previously). As shown in Fig. 2, for pharmaceutical yearly sales, antiallergic, analgesic, digestive, and antibiotic pharmaceuticals were dominant. Although excretion efficiencies vary with different pharmaceuticals, analgesics and psychotropics have low excretion efficiencies, indicating their possible lower priority in wastewater influent despite their higher sales data.

As shown in Table S2, pranlukast and carbocysteine are pharmaceuticals consumed in the greatest quantities, with 4080.3 t and 1372.6 t consumed per year, respectively. These high consumption levels could be attributed to the fact that Japan was the first country in the world to introduce pranlukast to the market for the treatment of bronchial asthma (Suissa and Ernst, 2003), and that the Japanese market has promoted use of carbocysteine as a well-known mucoactive and mucoregulatory drug (Ishiura et al., 2003). Moreover, the prevalence of asthma in Japan has been reportedly increasing (Fukutomi et al., 2011). The significant consumption of antagonist, mucolytic, and hypoglycemic pharmaceuticals is due to the aging population in Japan. Carballa et al. reported that the pharmaceutical consumed in the highest amount in Spain was ibuprofen (276.1 tons), and compared annual per capita consumption of 17 pharmaceuticals in different countries (Carballa et al., 2008). Ottmar et al. demonstrated that the top prescription rankings in the United States included lisinopril, atorvastatin, and amoxicillin (Ottmar et al., 2010). As expected, the consumption of active compounds varies strongly from country to country.

Although sales data on certain pharmaceuticals apparently indicate significant consumption levels, their discharge load rankings can be lower than their sales data rankings because of low excretion efficiencies. For example, PEC_{inf} of pranlukast was 257.0 μg/L with excretion efficiency of 86.6% (Down et al., 1974; Nakashima et al., 1993), indicating that pranlukast is the most prevalent pharmaceutical in wastewater influent. Although the yearly sale of rebamipide was 363.0 t, which is higher than that of iopamidol (309.9 t), the excretion efficiencies of rebamipide and iopamidol were 10% (Naito and Yoshikawa, 2010) and 100% (Pharmaceuticals and Medical Devices Agency, Japan), respectively, meaning that the PEC_{inf} of rebamipide (2.6 μg/L) was considerably lower than that of iopamidol (22.5 μg/L). Based on their excretion efficiencies, the PECs of pranlukast, ethyl icosapentate, carbocysteine, metformin, iopamidol, salicylic acid, acyclovir, iohexol, levofloxacin, and povidone iodine would be expected to have extremely high values in wastewater influent (> 10 μg/L), and 36 pharmaceuticals would be expected to have high concentrations in wastewater influent (> 1 μg/L). Among these pharmaceuticals with high concentrations, analgesics/anti-inflammatories and antibiotics appear to be the predominant groups in wastewater influent. Furthermore, some specific pharmaceuticals, such as allopurinol, were predicted for the first time in Japan (1.8 μg/L). Although the PEC of metformin in wastewater influent was predicted to be 24.1 μg/L, no study has yet evaluated its concentration in Japanese wastewater. In other studies, metformin was widely detected at a frequency of occurrence of 100% and an average concentration of 8.1 μg/L (Burns et al., 2018); the order of magnitude of its PEC in Japanese wastewater was similar to those reported in other countries (Oosterhuis et al., 2013; Tisler and Zwiener, 2018; Yan et al., 2019). Even though a wide variety of pharmaceuticals can be found in wastewater influent, it should be noted that not all their concentrations can be determined. Thus, the present study has provided a list of pharmaceuticals that warrant further investigation due to their high PEC values.

3.3. Evaluation of PEC in wastewater effluent

Table S3 in Supplementary material and Fig. 3 show that removal efficiencies of pharmaceuticals in Japanese WWTPs predicted by the EPI suite are within the range of, or less than observed removal efficiencies, allowing for considerable scatter in the results. According to the criteria in Table 1, the accurate level could be $0.5 < \text{ratio} < 2''$, and 19 compounds could be fit for the criteria in Fig. 3. The EPI suite adequately simulated the removal of biodegradable pharmaceuticals such as acetaminophen, naproxen, and ibuprofen (the ratios of their predicted removal efficiencies and observed removal efficiencies were 0.77, 1.91, and 1.16, respectively), which have high biodegradability and relatively weak sorption in WWTPs, as shown in previous studies (He et al., 2018; Min et al., 2018; Onesios et al., 2009; Tiwari et al., 2017). Estimated removals using the EPI suite were calculated from the biodegradability related to chemical structure and K_{oc} coefficients for sorption. From the perspective of chemical characteristics, the EPI suite performed better in estimating the removals of analgesics and hypolipidemic agents, such as acetaminophen, bezafibrate, naproxen, gemfibrozil, and ibuprofen (75.1%, 60.6%, 95.3%, 97.2%, and 94.9%, respectively).

Differences between reported and EPI estimated removal efficiencies were observed for antibiotics such as ciprofloxacin and clarithromycin; these antibiotics have poor biodegradability, but it has been previously found that they can be adsorbed in activated sludge (Min et al., 2018; Tiwari et al., 2017). In practice, it is difficult to predict accurately the sorption of pharmaceuticals in sludge, owing to factors such as pH in WWTPs (Ternes et al., 2004).

Discrepancies in removal efficiencies were observed by Verlicchi et al. (2012) who found that removal efficiencies in WWTPs were correlated to their characteristics, including biological reactor shape, operating conditions (solids retention time (SRT), hydraulic retention time (HRT), pH, redox conditions, etc.) and the water quality of the influent. Onesios et al. reported that removal of clarithromycin ranged from 0 to 54%, whereas the range of ofloxacin removal was from 23.8% to 94.0% (Onesios et al., 2009). Thus, in wastewater effluent, PEC calculations based on generalized data may be vulnerable to a high degree of inaccuracy because of different operating condition or wastewater composition (Choi et al., 2020). To compensate for these discrepancies, Coetsier et al. suggested adopting either the mean of a wide range of published data if available, or else considering an extreme

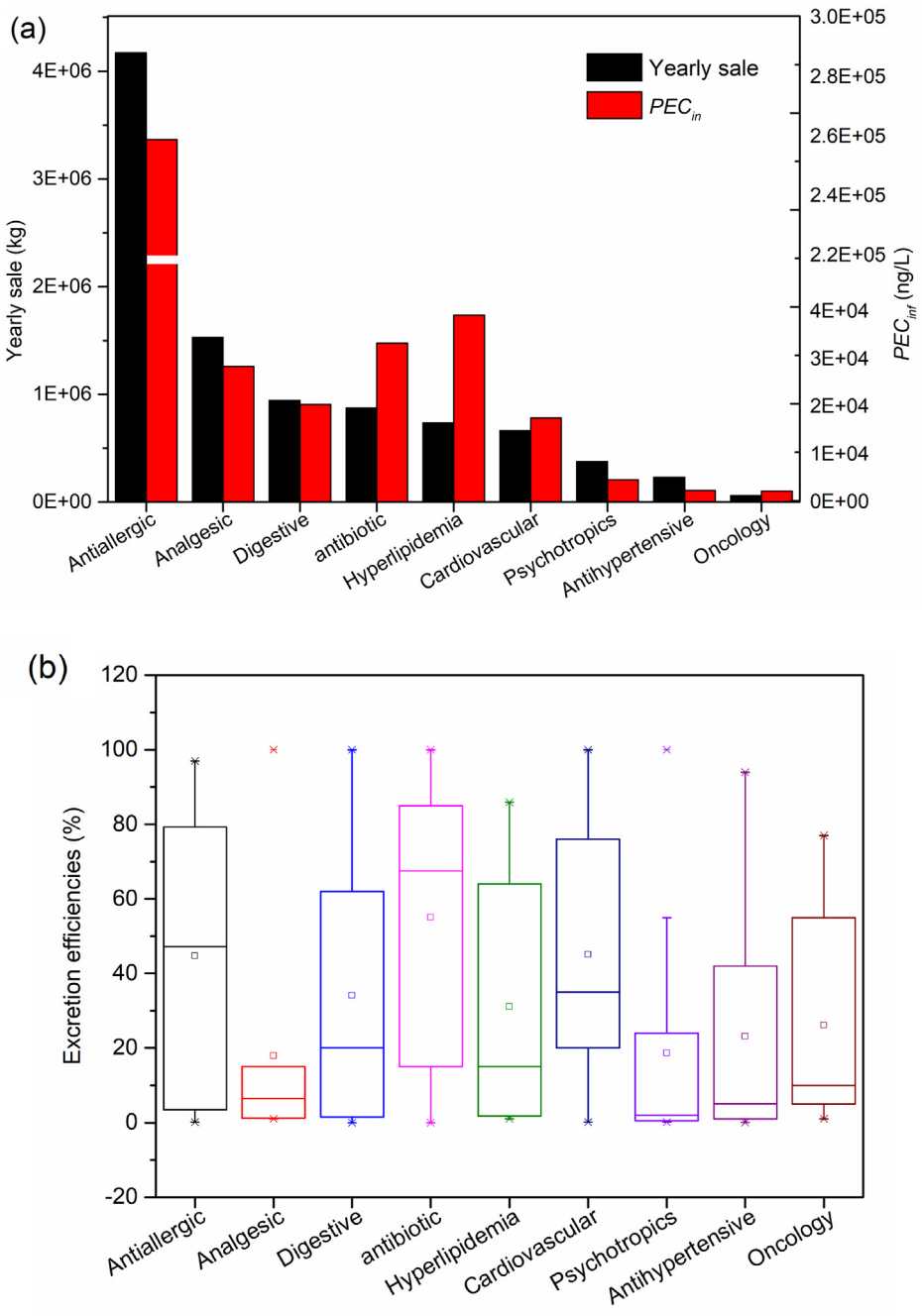

Fig. 2. Yearly sale loads and PECs in wastewater influent of pharmaceuticals by their classification (a), and the excretion efficiencies referring to the classification of pharmaceuticals (b).

scenario (Coetsier et al., 2009). Although the PEC could be overestimated, predicted removal efficiencies should be less than reported removal efficiencies. Turning to the extreme scenario concept, the results predicted by the EPI suite appear acceptable, as shown in Fig. 3, and so the EPI suite was applied herein to predict removal efficiencies.

After applying the predicted removal efficiencies and predicted concentrations in the influent (36 pharmaceuticals with high concentrations, > 1 μg/L as discussed above), the concentration of these pharmaceuticals in the effluent was predicted (Table S2 in Supplementary material), and Table S2 provides the full information of PECs in the influent and effluent of WWTPs. Among the selected pharmaceuticals, 26 pharmaceuticals were considered important in the effluent due to their high concentrations (> 1 μg/L), including 6 pharmaceuticals with concentrations in excess of 10 μg/L. Of these pharmaceuticals, the PEC of pranlukast in wastewater effluent was the most significant (203.8 μg/L) because of its low predicted removal efficiency by the EPI suite. Although the concentrations of several pharmaceuticals such as iopamidol and levofloxacin have been reported to be high in wastewater or receiving water in Japan (Azuma et al., 2018; Watanabe et al., 2016), the occurrence of other pharmaceuticals with high concentrations (i.e., povidone iodine, carbocysteine, and cefazolin) have not been reported in Japan previously, and these results provide a concerning list of pharmaceuticals that pose an environmental risk to aquatic environments. For those pharmaceuticals (> 1 μg/L) not measured in Japan, such as allopurinol, its PEC_{inf} and PEC_{eff} in this study were 1750.10, and 436.47 ng/L, respectively. In other countries, the PEC_{inf} of allopurinol was reported to be 1000 ng/L (Sedlak and Pinkston, 2011) and 4360 ng/L (Lacorte et al., 2018); and

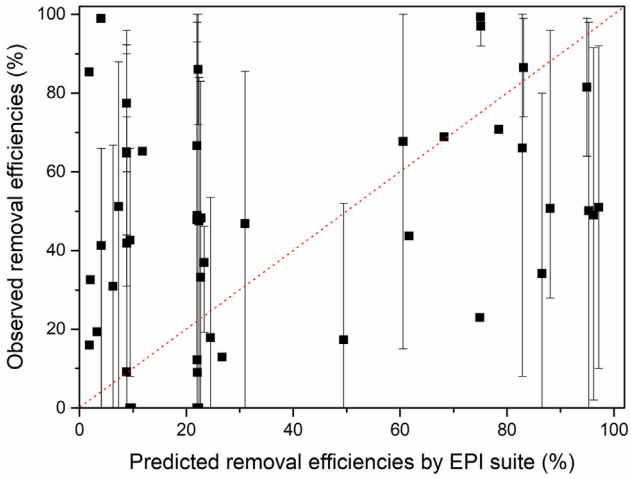

Fig. 3. Comparison between predicted (EPI suite) and measured (from open literature) removal efficiencies.

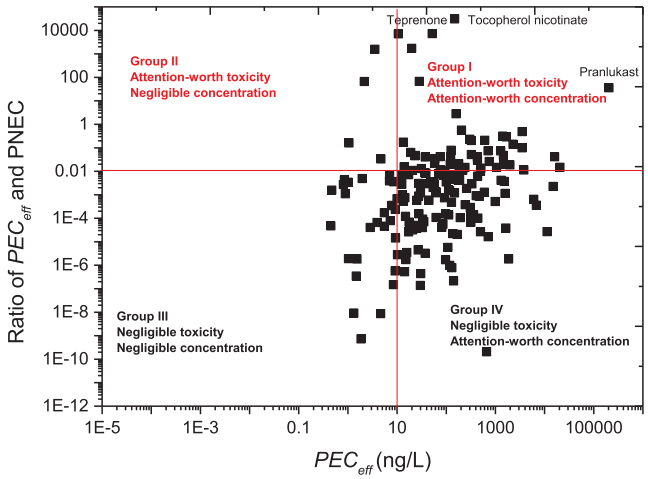

Fig. 4. PEC and environmental risk (ratio of PEC and PNEC) in wastewater effluent caused by the presence of pharmaceuticals.

the MEC_{inf} was reported as 600 ng/L (Grünebaum, 2011) and 3000 ng/L (Khan and Ongerth, 2004), as well as that its MEC_{eff} was 2000 ng/L (Khan and Ongerth, 2004) and 1700 ng/L (Gómez-Canela et al., 2019). Based on above values, similar concentration behavior of allopurinol was found in Japan and other countries. Furthermore, for famotidine, its PEC_{inf} and PEC_{eff} in this study were 1268.22, and 989.47 ng/L, respectively; its MEC_{inf} was reported to be 10–210 ng/L (Ahmed et al., 2017) and 273 ± 164 ng/L (Campos-Mañas et al., 2017); its MEC_{eff} was 132 ng/L with 84.0% of removal efficiency in membrane reactor (Dolar et al., 2012), and famotidine showed different influent concentration level in Japan from other countries. Therefore, the performance of pharmaceutical consumption can be evaluated by comparison of PEC or MEC in Japan and other countries.

At present, the EPI suite does not take into account the transformation and removal of pharmaceutical metabolites. From a risk assessment perspective, metabolites may be responsible for as much observed environmental toxicity as their parent compounds (Escher and Fenner, 2011). The EPI suite includes biodegradation and sorption in activated sludge but does not consider advanced treatment processes, such as ozonation, advanced oxidation process (AOP), and chlorination, which could lead to lower effluent concentrations.

3.4. Implication for environmental risk assessment

Environmental risk prioritization is important because it identifies the highest risk pharmaceuticals that warrant further investigation and monitoring (Guo et al., 2016). Evaluation of the PEC of pharmaceuticals and their PNEC calculated from the ECOSAR and KATE system showed that the PEC-to-PNEC ratios for 19 pharmaceuticals were above 0.1 (Table S2 in Supplementary material), indicating high toxicity in the aquatic environment, and 54 pharmaceuticals had ratios exceeding 0.01, indicating their toxicities should be evaluated in detail, including 19 pharmaceuticals with median toxicities (PEC-to-PNEC ratios above 0.1). It is worth noting that the environmental risks of several pharmaceuticals such as bezafibrate (0.074) and sulfamethoxazole (0.021) have been evaluated in previous Japanese studies (Komori et al., 2013), but the environmental risks of other pharmaceuticals, including tocopherol salt, teprenone, and azelnidipine, which were observed at high concentrations in Japanese wastewater effluent, have not previously been reported. The present study has provided a list of pharmaceuticals for which a comprehensive risk estimate is required. Fig. 4 classifies pharmaceuticals into four groups according to toxicity and concentration: (I) attention-worthy toxicity and attention-worthy concentration; (II) attention-worthy toxicity and negligible concentration; (III) negligible toxicity and negligible concentration; and (IV) negligible toxicity and attention-worthy concentration. From the perspective of safety, the risks posed by pharmaceuticals in groups I, II, and IV need to be evaluated in the future. For pharmaceuticals in categories (I) and (II), in order to alleviate the environmental risk, advanced treatments are suggested for their effective removals, including ozonation for triclosan (Orhon et al., 2017), and ozonated microbubbles for bicalutamide (Azuma et al., 2019a,b).

In summary, the present sale-based prediction method has provided acceptable estimates of influent pharmaceutical concentrations. The resulting predictions indicate the extent to which previous environmental analyses have ignored several of the most potentially problematic pharmaceuticals, such as pranlukast and carbocysteine. The STP script in the EPI suite proved useful in evaluating the significant discharge of pharmaceuticals from WWTPs, and in highlighting important pharmaceuticals in an extreme scenario. In particular, the occurrence of several pharmaceuticals, such as metformin, is noteworthy and requires further investigation, because these drugs exhibit high effluent concentration levels and pose significant potential environmental risks.

Besides providing the prediction of pharmaceuticals in wastewater system with their environmental risks, the limitations of this study were presented. First, Besides the difference between local consumption and national consumption of pharmaceuticals, unknown sources of pharmaceuticals discharge were unable to be applied in this study. Second, wastewater composition may affect the transformation of pharmaceuticals, which was not investigated due to the lack of data in the literature (Choi et al., 2020). Third, for pharmaceuticals, the transformation of metabolites was not considered in this study, for example, deglucuronidation of phase-II metabolites can result in higher concentrations of the parent compound, with higher measured environmental concentrations (Gauderat et al., 2016; Gao et al., 2018; He et al., 2019).

4. Conclusions

The present study has demonstrated that sales data of pharmaceuticals in Japan can be used for the prediction of pharmaceuticals in wastewater influent. The main findings are summarized as follows:

(1) According to reverse analysis of epidemiology for wastewater prediction, the PECs of 36 pharmaceuticals had high values in wastewater influent and so need further, detailed investigation. Pranlukast had the highest PEC in wastewater influent in Japan (257.0 μg/L).
(2) By applying the EPI suite to the prediction of pharmaceutical removals from wastewater systems and considering the most extreme

scenario, it was predicted that pranlukast was of greatest concern in wastewater effluent in Japan because of its resistance to biodegradation and its high consumption in the Japanese market. Moreover, 9 pharmaceuticals in the effluent exhibited potentially high toxicity according to the PEC/PNEC ratio, and 54 pharmaceuticals exhibited some toxicity. Therefore, further study is needed to explore the toxicity of these.

Overall, these findings provide confidence in the use of PECs in prioritization exercises for pharmaceuticals. Furthermore, the results prove that reverse analysis of epidemiology can be used widely in the future to predict environmental risk posed by pharmaceutical discharges. Beyond Japan, the proposed method could be applied to prioritization of pharmaceutical monitoring activities and environmental risk predictions in other countries.

CRediT authorship contribution statement

Kai He: Investigation, Formal analysis, Data curation, Writing - original draft. **Alistair G. Borthwick:** Data curation, Writing - review & editing. **Yingchao Lin:** Investigation, Formal analysis, Data curation. **Yuening Li:** Formal analysis, Data curation. **Jie Fu:** Methodology, Writing - review & editing. **Yongjie Wong:** Formal analysis, Data curation. **Wen Liu:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105690.

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